REMARKS

Declaration

The Examiner indicated that non-initialed and/or non-dated alterations have been made to the oath or declaration. A new non-altered declaration and power of attorney is being submitted herewith.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 64-135 are rejected as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner asserts the following.

> The claims also recite a "continuous stretch of 90 codons with no particular sequence associated with the claims (see also where the claims recite at least 80 base pairs). In addition, there is no indicia of what "portion thereof" of the protein is encoded by the synthetic nucleic acid. Further the specification asserts that in a preferred embodiment the nucleic acid sequence encoding a protein has at least 30, 50, 60, 75, 100, 200 or more non-common or less-common codons replaced with a common codon. The specification further asserts that in a preferred embodiment, the number of non-common or less-common codons replaced is less than 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 (see page 3, the same is said for the number of non-common or less-common codons remaining). Note that less than one can mean ½, 0, -1 etc. How can less than 1 codon that is non-common or less-common be replaced or remain if given the above numbers? In addition, it is recited in the claims and disclosed in the specification that at least one non-common or less-common codon is replaced, therefore, how can at least 1 be interpreted as less than 1, the two conditions are not equivalent. Note that at least 1 means nothing less than 1. Moreover, the specification asserts that at least 1 non-common or less common codons are replaced which includes 30, 50, 60, 75 or 100. Furthermore, if all these different conditions of at least 1, at least 30, 50... and less than 15, 14, 13...are all preferred embodiments as disclosed on page 3, how would one of skill in the art know what conditions to use to practice the claimed invention as they are not equivalent. Therefore, the invention is not adequately described as the

This rejection is respectfully traversed insofar as it may be applied to the presently amended claims. First, the Examiner's concern that the stretch of common codons recited in the claims is not associated with a particular sequence has been addressed by the present amendments to the claims. Claims 64-110 and 113-119, as presently amended, are directed to a synthetic nucleic acid sequence (or methods of making the same) which encodes a protein where at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence either: (a) includes at least 98% common codons in the sequence encoding the protein (claims 73-80, 89-96, 103-110 and 113-119); (b) includes a continuous stretch of at least 150 common codons and the continuous stretch encodes the protein or a fragment thereof (claims 64-68, 81-84, 97-99 and 113); or (c) includes a continuous stretch of common codons which includes at least 60% or more of the total codons and the continuous stretch encodes the protein or a fragment thereof (claims 69-72, 85-88, 100-102 and 113). Claims 111-112 and 120-135 cover vectors and cells that include the aforementioned synthetic nucleic acids. Thus, the present claims require that the common codons be part of the coding sequence for the protein recited in the claims.

Second, claims 67, 72, 75, 83, 87, 91, 99, 101 and 105 have been amended to recite that "between one and 15" non-common or less common codons remain in the sequence. This amendment obviates the Examiner's concern that the conditions recited in the claims are not equivalent. In light of the foregoing, Applicants submit that the specification provides sufficient support commensurate with the scope of the claims. Therefore, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

All the pending claims are rejected "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Each basis for the Examiner's rejection is addressed in turn below.

> Claim 64 and the dependent claims hereto are indefinite because the claim recites the replacement of less-common and non-common codons in a sequence that encodes a protein without indicating if the same protein will be encoded by the replacement codon (see also claims 69, 73, 85, 89, 97, 100, 103, 113, 116, 119, 120, 130 and 135). Also the claim does not require to a specific sequence in reciting "at least 90 codons"(see also claims 69, 73, 81, 85, 89, 97, 100, 103, 113, 114, 116, 119, 120, 125, 130 and 135).

This part of the rejection has been met by the present amendments to the claims. With regard to the examiner's concern that the claims do not indicate "if the same protein will be encoded by the replacement codon," claims 64, 69, 73, 85, 89, 97, 100, 103, 113, 120, 130 and 135 have been amended to recite that the non-common or less-common codon has been replaced by a common codon encoding the same amino acid as the non-common or less-common codon. However, the Examiner's rejection of claims 116 and 119 on this basis is unclear. Claim 116 does not contain "replacement" language and claim 119 already recites that the common codon encodes the same amino acid as the replaced non-common or less-common codon. Therefore, the Examiner is respectfully requested to clarify or withdraw this portion of the rejection with regard to claims 116 and 119.

With regard to the Examiner's assertion that the claims do not "require to a specific sequence in reciting 'at least 90 codons,'" claims 64, 69, 73, 81, 85, 89, 97, 100, 103, 113, 114, 116, 119, 120, 125, 130 and 135 have been amended to clarify that the stretch of replaced codons correlates to sequence of the recited protein.

> In a second aspect of the rejection, the examiner states that,
>
> Claim 67 is indefinite because the claim recites 'less than 15' and less than 15 means 14, 13, 10.6, 10.5, 1, ½, 0 or –1, etc. It is unclear for example how we can get a replacement of –1 codon or 0 (see also claims 72, 75, 83, 87, 91, 99, 101 and 105).

Applicants assert that, given the nature of the invention, it would be clear to one of ordinary skill in the art that the scope of the phrase "less than 15" would include only positive integers less than 15. Nonetheless, claims 67, 72, 75, 83, 87, 91, 99, 101, and [illegible]

In a third aspect of the rejection, the Examiner asserts the following.

> Claim 73 is indefinite because the claim recites "amino acids" instead of "amino acid residues" (see also claims 78, 89, 103 and 113). The claim is also indefinite for the recitation of "at least about 90 amino acids" note that "at least" is a narrow range and "about" is a broader range which goes outside the "at least" range (see also claim 85 where "comprise at least" is recited and "comprise" goes out side of "at least").

In response, claims 73, 78, 89, 103, 113, 114, 115 and 119 have been amended to recite "amino acid residues." Claims 73, 78, 89, 103, 113, 130 and 135 have been amended to replace the phrase "at least about. . ." with "at least." However, with respect to claim 85, Applicants respectfully traverse this aspect of the rejection. It is unclear to Applicants why the fact that "'comprise' goes out side of 'at least'" makes the claim indefinite, as "comprising" language is, by definition, open claim language, i.e., it always "goes outside" of the recited element. Claim 85, which recites "wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 33% of the codons of the synthetic nucleic acid sequence" is clear in that the synthetic nucleic acid has a continuous stretch of common codons that includes 33% or more of the codons of the sequence. Therefore, the Examiner is respectfully requested to clarify or to withdraw this basis of rejection of claim 85.

In another aspect of this rejection, the Examiner alleges that claim 82 is indefinite because "the claim recites the acronym 'BDD' without the spelled out word meaning." The Examiner also states that "[i]t is "presumed" that applicant meant to indicate that the factor VIII polynucleotide is inserted into a non-transformed cell and not the actual factor VIII (see also claims 86, 90 and 102). Applicants have amended claim 82 to spell out the phrase "beta domain deleted." Claims 82, 86, 90, 98, 102 and 104 have been amended to recite that the Factor VIII (or Factor IX) can be expressed in a non-transformed cell.

In yet another aspect of the rejection, the Examiner

method does not have this product as an endpoint." Claim 119 has been amended to recite the synthetic nucleic acid sequence as its endpoint.

In a further aspect of the rejection, claims 120, 125, 130 and 135 are said to be "indefinite for the recitation of 'vertebrate origin' as the claims do not indicate what organism. The claims are also indefinite for reciting 'that would occur' because it implies that there are times that the condition may not occur." This rejection has been met by the present amendments to the claims. Claims 120, 125, 130 and 135 have been amended to recite a primary or secondary mammalian cell and to delete the phrase "that would occur."

Finally, claim 120 is said to be "indefinite because the claim is not further limiting the independent claim (see also 126 and 131)." Since claim 120 is an independent claim, Applicants will assume that the Examiner meant to refer to claims 121, 126 and 131. These claims have been cancelled without prejudice.

Rejections Under 35 U.S.C. §103

Introduction

The present invention is directed to synthetic nucleic acids (and related methods and compositions) which have one or more of: a very long stretch of common codons; a very high percentage of common codons; or a stretch of common codons which is a very large percent of the total sequence. As discussed in detail below, the claimed nucleic acids are enriched with common codons to an extent not taught by the prior art. In fact, the art teaches away, and cautions one to not use the levels of codon replacement required by the present claims.

In a first aspect of the rejection, claims 64-119 are rejected as being unpatentable over Grantham et al. (Nucleic Acid Res. (1981) 9:r43-r74) (Grantham) taken with Seed et al. (U.S. Patent No. 5,795,737, August 18, 1998) (Seed '737) and Capon et al. (U.S. Patent No. 4,965,199, October 23, 1990) (Capon). The Examiner asserts that

method includes identifying non-preferred codons in the natural gene encoding the protein and replacing one or more of the non-preferred and less preferred codons with a preferred codon encoding the same amino acid as the replaced codon. Seed also teach that at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the codons in the natural gene are non-preferred codons (see column 2). As Seed teaches that one or more of the non-preferred or less-preferred codons are replaced with a preferred codon, a 33%, 94%, 98% or more codon replacement in a continuous stretch of the synthetic nucleic acid sequence is obtained as recited in the claims.

In addition, Seed teach that the synthetic gene encodes at least 50, 100, 150 or 500 contiguous amino acids of the protein (see columns 1-3). Seed further teaches that a large fragment of the codons of the human genes encoding Factor VIII and Factor IX are non-preferred codons or less-preferred codons. Replacement of a portion of these codons with preferred codons should yield genes capable of higher level expression in mammalian cell culture (se column 3).

Additionally, Seed teaches a vector and cell which includes a synthetic gene of the invention (see column 3). Seed also teaches a synthetic gene encoding the gp120 segment of HIV-1 (syngp120nM, see Figure 1A). According to Seed, in this synthetic gp120 gene nearly all of the native codons have been replaced with codons most frequently used in highly expressed human genes. Further, Seed teaches that this synthetic gene was assembled from chemically synthesized oligonucleotides of 150 to 200 bases in length (see column 8). Seed also teach that codon optimization is a fruitful strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes (see column 24). In-so-far as Seed do not teach a non-transformed cell as recited in claims 82, 86, 90 and 102, Capon teaches a method of producing Factor VIII in recombinant mammalian cells. As Capon teaches that human Factor VIII is produced in functional form in a particularly suitable host system. This system comprises baby hamster kidney cells which have been transfected with an expression vector comprising DNA encoding factor VIII (see abstract and column 5).

In view of the foregoing, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Grantham identifies the preferred/common codons and their frequency of use in different genes. Further, Grantham indicates that there is an association between codon choice and mRNA expressivity and Seed demonstrates this with the construction of synthetic genes. Seed used HIVgp120, the rat cell surface antigen Thy-1 and green fluorescent protein from *Aequorea victoria* to illustrate that codon optimization is a beneficial strategy for improving the expression in mammalian cells of a wide

> motivated to combine the above references to create a synthetic gene where one or more less-preferred or non-preferred codon is replaced by a common/preferred codon for codon optimization as taught by Seed, utilizing a host cell and expression vector as taught by Seed and Capon with a reasonably expectation of success because Grantham disclose that the amount of protein made by particular messenger depends on the choice of codons used,. Thus, the claimed invention was obvious to make and use at the time it was made and was prima facie obvious.

This aspect of the rejection is respectfully traversed insofar as it may be applied to the present claims. To establish prima facie obviousness of a claimed invention, the prior art must teach or suggest the invention, and the motivation to arrive at the present invention and a reasonable expectation of success must be found in the prior art. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). In this instance, a prima facie case of obviousness has not been made because the cited references, alone or in combination, fail to provide a teaching or motivation for a skilled artisan to arrive at the presently claimed synthetic nucleic acid sequences. Indeed, the art in fact teaches away from the present claims, as discussed below.

The present claims are directed to a synthetic nucleic acid sequence (or methods of making the same) which encodes a protein where at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence either: (a) includes at least 98% common codons (claims 73-80, 89-96, 103-110 and 113-119); (b) includes a continuous stretch of at least 150 common codons (claims 64-68, 81-84, 97-99 and 113); or (c) includes a continuous stretch of common codons which includes at least 60% or more of the total codons (claims 69-72, 85-88, 100-102 and 113). Claims 111-112 cover vectors and cells that include the aforementioned synthetic nucleic acids.

In contrast, Seed '737 provides only a generalized description of optimized nucleic acid sequences that neither teaches nor suggests synthetic sequences with the specific range of common codons as presently claimed. As indicated by the Examiner is the passage quoted above, Seed '737 discloses that "at least 10% 20% 30% 40% 50% 60% 70% 80%

present claims require that at least 98% of the codons of the synthetic sequence (or a continuous stretch including at least 150 codons or 60% of the total codons), must be common codons. Further, with regard to the claims that require that all the codons in a synthetic sequence be common codons (e.g., claims 68, 70, 77, 84, 88, 93, 96, 107 and 110), Seed is at best, silent and at worst, dissuasive. As Seed '737 explains, "It is not necessary to replace all less preferred or non-preferred codons with preferred codons. Increased expression can be accomplished even with a partial replacement." (See Seed '737, 3:1-5, emphasis added). With regard to the Factor VIII sequence, Seed asserts:

> A large fraction of the codons in the human genes encoding Factor VIII and Factor IX are non-preferred codons or less-preferred codons. Replacement of a portion of these codons with preferred codons should yield genes capable of higher level expression in mammalian cell culture. (See Seed '737, 3:34-40, emphasis added)

Thus, by focusing on partial replacement of non-preferred and less-preferred codons, Seed et al. provides neither the teaching nor the motivation for one skilled in the art to arrive at a synthetic sequence, much less a Factor VIII or Factor IX sequence, in which all the codons are common codons.

In addition, the Examiner argues that, "[a]s Seed teaches that one or more of the non-preferred or less-preferred codons are replaced with a preferred codon, a 33%, 94%, 98% or more codon replacement in a continuous stretch of the synthetic nucleic acid sequence is obtained as recited in the claims." Applicants respectfully disagree. Claims 64-72, 81-88, 97-102 and 113 do not require merely a continuous stretch of codons, but rather, the claims require a continuous stretch of common codons. Clearly, a disclosure of "one or more" non- or less-preferred codons replaced with a preferred or common codon hardly teaches or suggests a synthetic sequence having a continuous stretch of common codons of any length, much less a continuous stretch of either 150 codons or 60% of the total codons, as required by the claims. Indeed, the only reference to continuous or contiguous codons in Seed '737 is the passage referred to by the Examiner, which in its proper context, reads as follows.

> genes of the invention except that they encode only a portion of the protein. Such gene fragments preferably encode at least 50, 100, 150, or 500 contiguous amino acids of the protein (Seed '737, 3:21-26).

As can be seen, the use of "contiguous amino acids" in this passage refers merely to fragments of the synthetic genes described in the Seed '737 specification, i.e., the fragments are encoded by at least 50, 100, 150, or 500 contiguous codons. There is absolutely no teaching or suggestion, in this passage of Seed '737 or any other, that the "contiguous amino acids of the protein" must be encoded by contiguous common codons, as required by the present claims. Indeed, the disclosure of Seed et al. is so broad as to be meaningless to provide guidance or motivation for a skilled artisan to construct the synthetic nucleic acids within the specific ranges presently claimed with regard to the number of common codons.

Moreover, with regard to the claims that recite a synthetic optimized Factor VIII nucleic acid sequence (claims 81-96), the disclosure of Seed et al. is even more deficient. In fact, Seed '737 directly teaches away from the present invention, especially with regard to Factor VIII. In particular, at 3:27-29, Seed '737 states the following. "In constructing the synthetic genes of the invention it may be desirable to avoid CpG sequences as these sequences may cause gene silencing." In marked contrast, Applicants' disclosure teaches and claims an optimized synthetic beta domain deleted (BDD) Factor VIII nucleotide sequence in which all codons are common codons and in which "the GC content of the sequence increased from 44% to 64%" compared to the wild-type sequence (see page 43, lines 3-11 of the present application). Further, Applicants found that "systemic codon optimization (with disregard to CpG content) provides a fruitful strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes." See page 43, lines 25-28 of the specification (emphasis added). Thus, one of ordinary skill in the art would not have been motivated to construct a synthetic Factor VIII nucleic acid as presently claimed because modifying the Factor VIII sequence in such a way would have resulted in up to a 50% increase in the GC content of the nucleic acid sequence. Given the teachings of Seed '737, such a modification, at the time the application was filed, would have been predicted to cause gene silencing. Thus, Seed '737 [illegible]

The Examiner characterizes the secondary references as follows. Grantham shows that there is an association between codon choice and mRNA expressivity and Capon teaches the production of a Factor VIII in a recombinant mammalian host cell. But neither Grantham nor Capon make up for the deficiencies of Seed '737 in that neither reference provides the teaching, suggestion, or motivation missing from Seed '737. That is, neither reference teaches or suggests a synthetic nucleotide sequence with the specific range of common codons as presently claimed, i.e., a synthetic nucleic acid sequence that either: (a) includes at least 98% common codons; (b) includes a continuous stretch of at least 150 common codons; or (c) includes a continuous stretch of common codons which includes at least 60% or more of the total codons. Thus, neither Seed '737, Capon or Grantham, alone or in any combination, teach or suggest the present invention.

In another aspect of the rejection under 35 USC 103, claims 64-119 are rejected as being unpatentable over Kim et al. (Gene (1997) 199:293-301) (Kim) taken with Seed et al. (U.S. Patent No. 5,786,464, July 28, 1998) (Seed '464) and Capon. This portion of the rejection is respectfully traversed. Capon describes the production of a Factor VIII in a recombinant mammalian host cell. Seed '464, being a parent of the Seed '737 patent, contains a similar disclosure as that discussed above, except that Seed '464 does not contain a reference to Factor VIII or Factor IX as discussed above for Seed '737. However, the disclosure of Seed '464 is equally deficient as that of Seed '737, since Seed '464 also fails to provide a teaching, suggestion, or motivation to construct a synthetic nucleotide sequence with the specific range of common codons as presently claimed. According to the Examiner, Kim discloses:

> a study using mammalian cells and human erythropoietin genes (EPO), one in which native codons were systematically substituted with codons frequently found in highly expressed human genes and the other with codons prevalent in yeast genes.

As the Examiner indicates, Kim describes the replacement of native codons with yeast and human preferred codons, resulting in a hybrid gene. In contrast, the present claims require that the synthetic nucleic acid be optimized for human codons only. See Applicants' disclosure

particular amino acid in a human sequence. Kim et al. use preferred yeast codons because preferred yeast codons, unlike preferred human codons, are not as GC rich. Kim et al state:

> Re-engineered genes with human codon usage become high in their GC content. Although a low GC content of 5' UTR is ensured, optimizing the re-engineered gene further by decreasing the GC content of the limited region downstream of the initiator codon is advisable. (Kim, page 299, last paragraph)

Thus, Kim et al. in fact teach away from the present invention by suggesting that a synthetic nucleic acid sequence should not have a high percentage of human common codons. Far from decreasing the GC content of any region of the synthetic sequence, Applicants' presently claimed synthetic sequences (particularly the Factor VIII synthetic sequences, as discussed above) have substantially increased GC content compared to the non-optimized sequence. Applicants found that construction of such synthetic sequences, contrary to the teachings of the art, provide a fruitful strategy for protein expression with disregard to CpG content. (See Applicants' disclosure at page 43, lines 25-28). Therefore, neither Kim, Capon, nor Seed '464, alone or in any combination, teach or suggest all elements of the present claims.

In a further aspect of this rejection, claims 120-135 are rejected as being unpatentable over Grantham, taken with Seed '737 and Kuo et al. (U.S. Patent No. 5,045,455) (Kuo). As presently amended, claims 120-135 are directed to primary or secondary mammalian cells having an exogenous synthetic nucleic acid sequence which encodes a protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence either: (a) includes a continuous stretch of at least 150 common codons (claims 120-124 and 135); (b) includes a continuous stretch of common codons which includes at least 60% or more of the total codons (claims 125-129 and 135); or (c) includes at least 98% common codons (claims 130-135).

The Examiner asserts the following.

Although Grantham and Seed do not expressly teach a primary or secondary cell

> fragments (see column 3). One of ordinary skill in the art would be motivated to combine the above references because Seed teaches that expression of eukaryotic gene products in prokaryotes is sometimes limited by the presence of codons that re (*sic*) infrequently used and that expression of such genes can be enhanced by systematic substitution of the endogenous codons with codons over represented in highly expressed prokaryotic genes. Seed also teach that rare codons cause pausing of the ribosome, which leads to a failure to complete the nascent polypeptide chain and uncoupling of transcription and translation. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Applicants respectfully traverse this aspect of the rejection. As discussed above, neither Grantham or Seed '737 disclose or suggest a cell containing a synthetic nucleotide sequence with the specific range of common codons as presently claimed. On the contrary, as detailed above, Seed '737 clearly teaches away from the claimed invention, particularly with regard to the claims reciting Factor VIII. Kuo does not make up for the deficiencies of Grantham or Seed, as Kuo also does not disclose or suggest cells containing the synthetic nucleotide sequences recited in the present claims. Therefore, none of the cited references, alone or in combination, provide a disclosure or a motivation for a skilled artisan to arrive at the present claims.

In as much as there is no suggestion or teaching for combining the references proposed by the Examiner, Applicant respectfully submits that the references do not support a prima facie case of obviousness under the provisions of 35 USC §103. Therefore, Applicant respectfully contends that claims 64-135 are patentably distinguishable over the prior art of record. Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a Petition for Extension of Time and a check for the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 27 July 01

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Version with markings to show changes made

In the claims:

Claims 80, 95 and 109 have been cancelled.

Claims 64, 66, 67, 69, 72, 73, 75, 76, 78, 79, 81-83, 85-87, 89-92, 94, 97-106, 108, 113-116, 119, 120, 125, 130 and 135 have been amended as follows.

--64. (Amended) A synthetic nucleic acid sequence which encodes a protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence comprises a continuous stretch of at least [90]150 codons all of which are common codons, wherein said continuous stretch encodes the protein or a fragment thereof.

66. (Amended) The nucleic acid sequence of claim 64, wherein the continuous stretch comprises at least [95]200 common codons.

67. (Amended) The nucleic acid of claim 64, wherein the number of non-common or less-common codons [replaced or] remaining is [less than]between one and 15.

69. (Amended) A synthetic nucleic acid sequence which encodes a protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence comprises a continuous stretch of common codons which

72. (Amended) The nucleic acid of claim 69, wherein the number of non-common or less-common codons replaced or remaining is [less than]between one and 15.

73. (Amended) A synthetic nucleic acid sequence which encodes a protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and wherein at least [94%]98% or more of the codons in the sequence encoding the protein are common codons and wherein the [synthetic nucleic acid sequence encodes a] protein [of] is at least [about] 90 amino [acids]acid residues in length.

75. (Amended) The nucleic acid of claim 73, wherein the number of non-common or less-common codons replaced or remaining is [less than]between one and 15.

76. (Amended) The nucleic acid of claim 73, wherein the non-common and less-common codons, taken together, replaced or remaining, are equal or less than [6%]2% of the codons in the synthetic nucleic acid sequence.

78. (Amended) The nucleic acid of claim 73, wherein the nucleic acid sequence encodes a protein of at least [about] 105 amino [acids]acid residues in length.

79. (Amended) The nucleic acid of claim 73, wherein at least [96%]99% of the

81. (Amended) A synthetic nucleic acid sequence which encodes Factor VIII, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least [90]150 codons all of which are common codons, wherein said continuous stretch encodes the Factor VIII or a portion thereof.

82. (Amended) The synthetic nucleic acid sequence of claim 81 where the factor VIII protein has one or more of the following characteristics:

a) the B domain is deleted (beta domain deleted (BDD) factor VIII);

b) it has a recognition site for an intracellular protease of the PACE/furin class; or

c) it is [inserted into]expressed in a non-transformed cell.

83. (Amended) The synthetic nucleic acid sequence of claim 81, wherein the number of non- common or less- common codons replaced or remaining is [less than]between one and 15.

85. (Amended) A synthetic nucleic acid sequence which encodes Factor VIII, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least [33%]60% of the codons of the synthetic nucleic acid sequence, wherein said continuous stretch encodes the Factor VIII or a portion thereof.

a) the B domain is deleted (BDD factor VIII);

b) it has a recognition site for an intracellular protease of the PACE/furin class; or

c) it is [inserted into]expressed in a non-transformed cell.

87. (Amended) The synthetic nucleic acid sequence of claim 85, wherein the number of non- common or less- common codons replaced or remaining is [less than]between one and 15.

89. (Amended) A synthetic nucleic acid sequence which encodes Factor VIII, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least [94%]98% or more of the codons in the sequence encoding the Factor VIII are common codons and the [synthetic nucleic acid sequence encodes a] Factor VIII [of]is at least [about] 90 amino [acids]acid residues in length.

90. (Amended) The synthetic nucleic acid sequence of claim 89 where the factor VIII protein has one or more of the following characteristics:

a) the B domain is deleted (BDD factor VIII);

b) it has a recognition site for an intracellular protease of the PACE/furin class; or

c) it is [inserted into]expressed in a non-transformed cell.

91. (Amended) The synthetic nucleic acid sequence of claim 89, wherein the number of non- common or less- common codons replaced or remaining is [less than]between one and 15.

92. (Amended) The synthetic nucleic acid sequence of claim 89, wherein the number of non- common or less- common codons replaced or remaining, taken together, are equal or less then [6%]2% of the codons in the synthetic nucleic acid sequence.

94. (Amended) The synthetic nucleic acid sequence of claim 89, wherein at least [96%]99% of the codons in the synthetic nucleic acid sequence are common codons.

97. (Amended) A synthetic nucleic acid sequence which encodes Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least [90]150 codons all of which are common codons, wherein said continuous stretch encodes the Factor IX or a portion thereof.

98. (Amended) The synthetic nucleic acid sequence of claim 97, wherein the factor IX protein has one or more of the following characteristics:

a) it has a PACE/furin site at a pro-peptide mature protein junction; or

b) is [inserted into]expressed in a non-transformed cell.

99. (Amended) The synthetic nucleic acid sequence of claim 97, wherein the number of non- common or less- common codons replaced or remaining is [less than]between one and 15.

100. (Amended) A synthetic nucleic acid sequence which encodes Factor IX, wherein at least one non-common or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon

the synthetic nucleic acid has a continuous stretch of common codons which comprise at least [33%]60% of the codons of the synthetic nucleic acid sequence, wherein said continuous stretch encodes the Factor IX or a portion thereof.

101. (Amended) The synthetic nucleic acid sequence of claim 100, wherein the number of non- common or less- common codons replaced or remaining is [less than]between one and 15.

102. (Amended) The synthetic nucleic acid sequence of claim 100, wherein the factor IX protein has one or more of the following characteristics:

a) it has a PACE/furin site at a pro-peptide mature protein junction; or

b) is [inserted into]expressed in a non-transformed cell.

103. (Amended) A synthetic nucleic acid sequence which encodes Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least [94%]98% or more of the codons in the sequence encoding the Factor IX are common codons and the [synthetic nucleic acid sequence encodes a] Factor IX [of]is at least [about] 90 amino [acids]acid residues in length.

104. (Amended) The synthetic nucleic acid sequence of claim 103, wherein the factor IX protein has one or more of the following characteristics:

a) it has a PACE/furin site at

105. (Amended) The synthetic nucleic acid sequence of claim 103, wherein the number of non- common or less- common codons replaced or remaining is [less than]between one and 15

106. (Amended) The synthetic nucleic acid sequence of claim 103, wherein the number of non- common or less- common codons replaced or remaining, taken together, are equal or less then [6%]2% of the codons in the synthetic nucleic acid sequence.

108. (Amended) The synthetic nucleic acid sequence of claim 103, wherein at least [96%]99% of the codons in the synthetic nucleic acid sequence are common codons.

113. (Amended) A synthetic nucleic acid sequence which encodes a protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and having the following properties:

(i) the synthetic nucleic acid sequence comprises a continuous stretch of at least [90]150 codons all of which are common codons, wherein said continuous stretch encodes the protein or a fragment thereof;

(ii) the synthetic nucleic acid sequence comprises a continuous stretch of common codons, which continuous stretch includes at least [33%]60% or more of the codons in the synthetic nucleic acid sequence, wherein said continuous stretch encodes the protein or a fragment thereof; and

(iii) wherein at least [94%]98% or more of the codons in the sequence encoding the protein are common codons and wherein the [synthetic nucleic acid sequence encodes a]

114. (Amended) A method for preparing a synthetic nucleic acid sequence which is at least 90 codons in length, comprising:

identifying a non-common codon and a less-common codon in a non-optimized gene sequence which encodes a protein and is at least 90 codons in length; and

replacing at least [94%]98% of the non-common and less-common codons with a common codon encoding the same amino acid residue as the replaced codon.

115. (Amended) The method of claim 114, wherein at least [98%]99% of the non-common and less-common codons are replaced with a common codon encoding the same amino acid residue as the replaced codon.

116. (Amended) A method for making a nucleic acid sequence which directs the synthesis of an optimized message of a protein of at least 90 amino acids comprising:

synthesizing at least two fragments of [the]a nucleic acid sequence, wherein the two fragments encode adjoining portions of [the]a protein of at least 90 amino acids and wherein both [subunits]fragments are mRNA optimized; and

joining the two fragments such that a non-common codon is not created at a junction point, thereby making the mRNA optimized nucleic acid sequence.

119. (Amended) A method for preparing a synthetic nucleic acid sequence encoding a protein which is at least 90 [codons]amino acid residues in length, comprising identifying non-common codon and less-common codons in the non-optimized [gene]nucleic acid sequence encoding [the]a protein of at least 90 amino acid residues in length and replacing at least

replaced codon, thereby preparing a synthetic nucleic acid sequence encoding a protein which is at least 90 amino acid residues in length.

120. (Amended) A primary or secondary mammalian cell [of vertebrate origin] having an exogenous synthetic nucleic acid sequence which encodes a protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least [90]150 codons all of which are common codons, wherein said continuous stretch encodes the protein or a portion thereof; is at least 80 base pairs in length and is free of unique restriction endonuclease sites [that would occur] in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the protein or polypeptide product.

125. (Amended) A primary or secondary mammalian cell [of vertebrate origin] having an exogenous synthetic nucleic acid sequence which encodes a protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least [33%]60% of the codons of the synthetic nucleic acid sequence, wherein said continuous stretch encodes the protein or a portion thereof; is at least 80 base pairs in length and is free of unique restriction endonuclease sites [that would occur] in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the protein or polypeptide product.

[illegible] synthetic nucleic acid [illegible] wherein

at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least [94%]98% or more of the codons in the sequence encoding the protein are common codons and the [synthetic nucleic acid sequence encodes a] protein [of]is at least [about] 90 amino acids in length; it is at least 80 base pairs in length and is free of unique restriction endonuclease sites [that would occur] in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the protein or polypeptide product.

135. (Amended) A primary or secondary mammalian cell [of vertebrate origin] having an exogenous synthetic nucleic acid sequence which encodes a protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has the following properties: it has a continuous stretch of at least [90]150 codons all of which are common codons, wherein said continuous stretch encodes the protein or a portion thereof; it has a continuous stretch of common codons which comprise at least [33%]60% of the codons of the synthetic nucleic acid sequence, wherein said continuous stretch encodes the protein or a portion thereof; at least [94%]98% or more of the codons in the sequence encoding the protein are common codons and the [synthetic nucleic acid sequence encodes a] protein [of]is at least [about] 90 amino acids in length; it is at least 80 base pairs in length and which is free of unique restriction endonuclease sites [that would occur] in the message optimized sequence; and

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the protein or polypeptide product.--